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EXAMINER

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NAME	ART UNIT	PAPER NUMBER
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HMI2/3d2e

16035

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DATE MAILED:

10/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/439,293

Applicant(s)

Cabot et al

Examiner

Zara, Jane

Group Art Unit

1635

Responsive to communication(s) filed on _____.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-20 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

NOTICE TO COMPLY WITH SUBSEQUENT REQUIREMENTS

... SEE OFFICE ACTION ON THE FOLLOWING PAGES ...

File copy

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DETAILED ACTION

Claims 1-20 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 8, 9, 15 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "an antisense glycosylceramide synthase compound" should be rewritten to refer more explicitly to an antisense which is targeted to the gene encoding (i.e. human or mouse) glycosylceramide synthase of a particular sequence, whereby the sequence is identified by an appropriate SEQ ID No. and whereby the corresponding sequence and SEQ ID No. has been disclosed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing adriamycin and ceramide-6 sensitivity in MCF-

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7-AdrR cells *in vitro* comprising the introduction of the antisense molecule of Figure 1, which is targeted to the sequence of human glucosylceramide synthase originally disclosed by Ichikawa et al and referenced on page 11 of the specification in Proc. Natl. Acad. Sci. USA, 93: 4638-4643, does not reasonably provide enablement for a method of reversing drug resistance to all drugs and inducing apoptosis in all cancer cells comprising the introduction of any and all antisense targeting all glucosylceramide synthase genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is drawn to compositions and methods of reversing drug resistance and inducing apoptosis in a cancer cell *in vivo* comprising the introduction of an antisense targeting glucosylceramide synthase and further comprising contacting the cell with a chemosensitizer or chemotherapeutic agent.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery, expression and/or inhibition is in its infancy and highly unpredictable.

The nature of the invention. Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered therapy per se, *in vivo* delivery shares many of the obstacles recognized

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for the actual therapy methods because successful therapy methods are for the most part based on the ability to delivery exogenous nucleic acids to cells or tissues of interest.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery as it pertains to the instant application. Verma et al teach the problems of gene delivery in whole organisms using non-viral vector approaches (i.e. including liposomes as delivery agents) and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teach that the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids including antisense is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant glucosylceramide synthase gene.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of reversing all drug resistance in all cancer cells *in vitro* or *in vivo*, nor of inducing apoptosis in any and/or all cancer cells, which methods comprise the introduction of an

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antisense which is targeted to glucosylceramide synthase and further comprise contacting the cell with a chemosensitizer or a chemotherapeutic agent. Furthermore, applicants have not provided adequate guidance in the specification toward said methods in any and all organisms which would avoid the technical obstacles recognized in the art as described above.

The specification teaches a method of increasing adriamycin and ceramide-6 sensitivity in MCF-7-AdrR cells *in vitro* comprising the introduction of the antisense molecule which is targeted to the sequence of human glucosylceramide synthase originally disclosed by Ichikawa et al and referenced on page 11 of the specification in Proc. Natl. Acad. Sci. USA, 93: 4638-4643, and which is schematically depicted in figure 1. The specification fails to teach the successful delivery of antisense and subsequent inhibition of glucosylceramide synthase in a whole organism whereby the gene is inhibited and treatment is provided. The specification fails to teach the induction of apoptosis in any cancer cells *in vitro* or in a whole organism. In addition, the specification fails to teach the co-administration of antisense and any and/or all chemotherapeutic or chemosensitizing agents *in vivo* whereby treatment effects are provided, nor does the specification teach the co-administration of antisense and all chemotherapeutic or chemosensitizing agents to all cancer cells *in vitro*. The specification as filed teaches only the co-administration of antisense targeted to glucosylceramide synthase and adriamycin to adriamycin resistant MCF-7 cells *in vitro*, whereby the gene is inhibited and caspase-3 is induced. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the co-administration of antisense targeted

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to glucosylceramide synthase and any and/or all chemotherapeutic or chemosensitizing agents *in vivo* whereby the gene is inhibited and further where treatment effects are provided in view of the lack of guidance in the specification and the known unpredictability associated with the administration and *in vivo* delivery of antisense as cited in the references of Friedmann, Verma et al, Schofield et al, Branch and Crooke. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant glucosylceramide synthase gene, nor of the effects of co-administration of said antisense with any and/or all chemosensitizing or chemotherapeutic agents in a whole organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to the compositions and methods of reversing drug resistance and inducing apoptosis in any cancer cell *in vivo* comprising the introduction of an antisense targeting glucosylceramide synthase and further comprising contacting the cell with a chemosensitizer or chemotherapeutic agent. In order to practice the invention over the scope claimed, it would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of an antisense and the co-administration of a chemosensitizer or chemotherapeutic agent to an organism such that glucosylceramide synthase is inhibited and further where treatment effects can be provided. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target

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sites, modes of delivery and formulations to target appropriate cells and tissues harboring glucosylceramide synthase such that the gene is inhibited *in vivo*, apoptosis is induced and drug sensitivity is increased in the target cells and further that treatment effects are provided. Since the specification fails to provide any particular guidance for the successful delivery of antisense and the co-administration of a chemosensitizer or chemotherapeutic agent in any and/or all organisms, and since determination of these factors for a particular antisense, chemosensitizer and chemotherapeutic agent in a particular organism with a particular cancer is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(a) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ichikawa et al in view of Lavie et al and further in view of Milner and James insofar as the claims are drawn to a method of reversing drug resistance in a cancer cell in vitro comprising the administration of an antisense specifically targeting glucosylceramide synthase.

Ichikawa et al teach the DNA sequence and functional expression of human glucosylceramide synthase (figure 6, page 4642).

Ichikawa et al do not teach the generation of antisense targeted to human glucosylceramide synthase.

Lavie et al teach the correlation between increased levels of glucosylceramide and drug resistance in cells (see entire text, especially abstract and figure 8, page 19,534).

Milner et al and James teach methods of making antisense oligonucleotides to a desired target gene in any region, including the 5' or 3' untranslated regions (see entire texts and see James especially at pages 197-198).

It would have been obvious to one of ordinary skill in the art to engineer antisense oligonucleotides to glucosylceramide synthase since the sequence had been disclosed by Ichikawa et al. One of ordinary skill in the art would have been motivated to generate antisense to inhibit glucosylceramide synthase, since the motivation to generate cells which are deficient in glucosylceramide synthase had been disclosed by Ichikawa et al (last paragraph, page 4643), and

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the technology to generate antisense targeting a gene of known sequence was known to those of ordinary skill in the art, as had been taught by Milner et al and James. Furthermore, one of ordinary skill in the art would have been motivated to inhibit the synthesis of glucosylceramide in drug resistant cells because it had been taught in the prior art by Lavie et al that a correlation existed between cellular drug resistance and increased levels of glucosylceramide, and hence one of ordinary skill in the art would have expected that the inhibition of the enzyme glucosylceramide synthase would lead to a decrease in the reaction product, glucosylceramide.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Specification

On page 28, third line from the end of the first paragraph, the word "trance" should be replaced by "trace".

On page 2, the number "19536271" should be removed from the third line of the second paragraph.

On page 22, a SEQ. ID No. must be inserted into the text which identifies the antisense sequence targeted to glycosylceramide synthase (i.e. that was inserted into the expression vector).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent

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Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. See the accompanying Notice to Comply.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
April 24, 2000

Remy Yucel
REMY YUCEL, PH.D
PATENT EXAMINER